REMARKS

Claims 24-28 are pending in the Subject Application. Claim 24 has been amended.

Support for amended claim 24 can be found throughout the Specification, see for example, Example 11 beginning on Page 26.

THE TELEPHONE INTERVIEW

Applicants wish to thank Supervisory Special Examiner (SPE) David Nguyen for the telephone interviews of November 1st and November 8th. In the telephone interview, Supervisory Special Examiner (SPE) David Nguyen indicated that claims to the use of human BMP-2 transduced MSC administered to allogeneic recipients would be allowable, if the Applicants submitted a response amending the claims as such, and indicating the unexpected nature of the results of the Subject Application, and a Declaration describing the same.

REJECTION UNDER 35 U.S.C. § 103:

In the Office Action, the Examiner rejected claims 24-28 under 35 U.S.C. § 103 as allegedly being rendered obvious in view of Ahrens, and further in view of Bonadio et al, and Lee et al. The Examiner alleged that claims to the use of *ex-vivo* transduced/transfected mesechymal stem cells expressing BMP-2, for inducing organized functional bone formation at a site of bone infirmity are obvious in view of Bonadio, as allegedly Figure 8 of Bonadio shows organized formation at the rejoin of the break. The Examiner alleged that Ahrens describes use of mesenchymal stem cells transduced/transfected with a BMP-2 construct, and that Bonadio describes the usefulness of applying such cells to a site of bone infirmity. The Examiner further alleged that for the art to render claims obvious, the art "need provide a motivation to induce bone formation at a site of bone infirmity using the method of the claimed invention".

Applicants maintain that such motivation be credible, and address the unexpected findings of the instant invention. Accordingly, Applicants maintain that none of the cited references render the claimed invention obvious, contrary to the Examiner's allegation.

Applicants maintain that Ahrens et al, in view of Bonadio and Lee, are not credibly combined to describe ex-vivo cultured MSC transduced/transformed with a BMP-2, for

inducing bone formation, and that Applicants demonstration of organized bone formation along defect edges in Example 11 herein is unexpected.

Ahrens provides no basis for stimulation of bone formation *in vivo* at a site of bone infirmity by MSC expressing BMP-2. Ahrens disclosure is limited to *in vitro* responses of progenitor cells to a BMP and other osteoinductive compounds. One skilled in the art based on Ahrens has no insight on the likelihood that implantation *of ex-vivo* cultured progenitor cells, expressing BMP-2 alone, will stimulate bone formation, and align along bone defect edges in doing the same. Professor Edward Schwartz attests in the attached declaration (hereinafter "the declaration") (Appendix 1) that appropriate cell homing and orientation along the defect edges is a result, which could not have been foreseen, based on Ahrens. Applicants note, in particular, that progenitor cells alone localized to connective tissue, and only progenitor cells transduced with a vector expressing BMP were found within newly formed bone trabecules (Page 26, last paragraph).

Applicants maintain that Bonadio, further in view of Ahrens does not render obvious bone formation at a site of injury, as a result of implantation *of ex-vivo* cultured progenitor cells expressing BMP-2 alone. Although Bonadio suggests, based on his gene transfer experiments, that bone progenitor cells would be useful in stimulating bone formation, such suggestion is merely speculative. Bonadio targets a heterogeneous population of cells and not progenitor cells, wherein stem cells if present are in a negligible amount. Uptake of DNA by progenitor cells of the present invention *in situ*, is known to one skilled in the art to be drastically reduced (Rebel V.I. et al., Stem Cells (2000) 18: 176-82; Zhao Q. et al., Blood (1994) 84:3660-6). It is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art". *In re Wesslau, 353 F.2d at 241, 147 U.S.P.Q. at 393.* One of ordinary skill in the art, based on the knowledge in the art at the time of the invention, and based on Bonadio's description, would not accept Bonadio's contention of targeting progenitor cells as credible. Thus one skilled in the art would not accept that Bonadio provides appropriate motivation to use Ahrens' (or Lee's as described below) cells for stimulating bone formation.

Moreover, Applicants have herein demonstrated that unexpectedly, only MSC expressing BMP-2 (MSC-BMP-2) provided superior bone formation, which aligned along the

bone defect edge. Surprisingly, only MSC-BMP-2 yielded such superior effects, this despite the fact BMP-2 was secreted at a roughly 100 times lower concentration than that of CHO cells transduced to express BMP-2 and 100 times lower concentration than the amount of BMP-2 loaded on collagen sponges. Despite significant reduction in BMP-2 secretion, nonetheless, only MSC-BMP-2 appropriately homed to the site of injury, aligned along defect edges, was incorporated in newly formed bone trabecules, and formed superior quantitative and qualitative bone, with less bone resportion, as compared to non-transduced MSC, or CHO-BMP-2, or sites of implantation of collagen sponges comprising the BMP-2 alone.

Lee, similar to Ahrens does not provide any demonstration of bone formation, but rather production of alkaline phosphatase alone, *in vitro*, and comprises all of the limitations described above with regard to Ahrens. Therefore, implantation of an enriched MSC population expressing BMP-2 promoting organized bone formation, within the boundaries of the fracture edges, with no bone resorption is an unexpected finding in view of any of the references cited, alone or in combination.

The Declaration of Professor Edward Schwartz attached hereto attests to the unexpected nature of the findings, and the fact that the cited references do not render such findings obvious.

In addition, the Examiner has also rejected claims 24-27 in view of the above cited references, further in view of Wozney (US Patent No. 6,291,206), under 35 USC 103.

Applicants respectfully disagree. As stated in the attached declaration, Wozney describes the expression of BMP receptor for BMP-2 in cells responding to the growth factor with no description of the utility for *ex-vivo* cultured transduced/transformed with BMP-2, in inducing organized functional bone formation at a site of bone infirmity. Applicants maintain that since Ahrens, Lee and Bonadio do not render obvious the methods of inducing functional bone formation via implanting ex-vivo cultured MSC transfected with BMP-2, its further combination with Wozney does not render obvious use of such cells further comprising a BMP-2 receptor, and accordingly request withdrawal of the rejection.

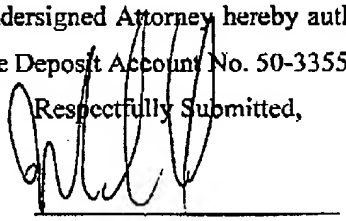
In addition the Examiner rejected claims 24-28 in view of the above cited references, further in view of Hattersley, under 35 USC 103.

Applicants respectfully disagree. Hattersley, similar to Wozney does not describe, nor provide any foundation for *ex-vivo* cultured MSC transduced/transformed with BMP-2, in inducing organized functional bone formation at a site of bone infirmity. Applicants maintain that since Ahrens, Lee and Bonadio do not render obvious the methods of inducing functional bone formation via implanting ex-vivo cultured MSC transfected with BMP-2, its further combination with Hattersley does not render obvious use of such cells further comprising a PTH/PTH receptor. Accordingly, Applicants request withdrawal of the rejection.

Based on the foregoing, the pending claims are deemed to be allowable. Their favorable reconsideration and allowance is respectfully requested. Should the Examiner have any question or comment as to the form, content or entry of this Amendment, the Examiner is requested to contact the undersigned at the telephone number below.

Should any fee be due, the undersigned Attorney hereby authorizes the United States Patent and Trademark Office to charge Deposit Account No. 50-3355 for any fees required.

Respectfully Submitted,



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